REMARKS

Amendments to the Specification

A. Trademarks

The Examiner requests that each letter of all trademarks be capitalized and accompanied by the generic terminology. In response, the specification has been amended accordingly.

B. Drawings

The Examiner objects to the Drawings and contends that Figures 1-4 are not identified with Figure Numbers. Applicants respectfully point out that substitute Drawings (Figures 1-4) with appropriate indicia were submitted with the Response to Notice to File Missing Parts filed June 12, 2002.

The Examiner further objects to Figure 1 because the designations found on the graph, *e.g.*, PV1 12130RU and mCD28.Fc, are not sufficiently explained in the text. Applicants traverse this objection and submit that the designations in Figure 1 would be clear to one of ordinary skill in the art. Nevertheless, the specification has been amended at page 48, second paragraph, in the description of Example 1, to explain more specifically the designations in Figure 1.

C. Informalities

The Examiner objects to the specification for various informalities. Specifically, the Examiner objects to the recitation at page 48, first paragraph, of "whole anti-CD28 antibody," because the Examiner contends that Examples 1-4 "apparently do not reference a 'whole anti-CD28 antibody.'" The Examiner continues that although Example 1 mentions "anti-CD28 (PV1.10.17)," the nature of the referenced compound is unclear.

Applicants respectfully point out that PV1, also referred to as "PV1.10.17," is a whole anti-CD28 antibody. The whole anti-CD28 antibody PV1 (or PV1.10.17) is described in Example 1 of U.S. Patent No. 5,948,893, reference to which can be found in the instant application at least at page 3, second paragraph, page 18, last paragraph and page 28, last

paragraph. Nevertheless, the specification has been amended at page 48, first through fifth paragraph, to clarify that the whole anti-CD28 antibody used in the Examples is PV1, and that this antibody is also referred to as PV1.10.17.

The Examiner further objects to the designation of 710-Fab as unclear. Additionally, the Examiner objects to the reference to "control mice" in Example 4 and Figure 4, and contends that the nature of the treatment if any received by the control mice is not disclosed.

Applicants traverse these objections. The Examiner's objections to the specification for an alleged lack of clarity of particular aspects of experiments disclosed, such as the nature of the treatment received by control mice, are objections to the data provided in the working examples. Applicants note that the MPEP makes clear that working examples are not required for an invention to be enabled. An example may be "working" or prophetic. Moreover, an applicant need not have actually reduced the invention to practice prior to filing. MPEP 2164.02. The instant specification nevertheless provides working examples which demonstrate that PV1 scFv inhibits T cell responses *in vitro,* and delays disease onset in a mouse model for diabetes *in vivo*. Applicants maintain that the metes and bounds of the currently claimed invention would be clear to one of skill in the art. In view of at least the foregoing, Applicants respectfully request that the Examiner withdraw these objections to the specification.

Amendments to the Claims

Claims 1-24 are pending in the application. Claims 5, 13 and 21 have been canceled, without prejudice, as being drawn to a non-elected invention. Claims 1, 6-9, 14-16 and 22-24 have been amended. New claim 25-27 has been added. Accordingly, Claims 1-4, 6-12, 14-20 and 22-27 will be pending upon entry of the instant Amendment.

Support for the foregoing amendments is found throughout the specification and claims as originally filed. Specifically, support for the recitation of "an isolated antigen binding portion of an anti-CD28 antibody" can be found at least at page 9, second paragraph, and in particular at lines 11-12, and at pages 13-14, bridging paragraph. Support for new claims 25-27 can be found at least at page 9, lines 14-16 and lines 21-26.

No new matter has been added by way of these amendments. Amendment to the claims should in no way be viewed as acquiescence to any rejection. Applicants reserve the right to pursue the claims as originally filed in this or subsequent applications.

Information Disclosure Statement

The Examiner has requested Applicants to resubmit the references A2, A5, A6, B2 and B6 listed on the IDS filed October 28, 2002. In response, Applicants provide herewith copies of said references. Accordingly, Applicants respectfully request the Examiner to initial and return the PTO form 1449 pertaining to these references.

Rejection of Claims 1, 2, 6-10 and 14-16 Under 35 U.S.C. 102(b)

Claims 1, 2, 6-10 and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Linsley *et al.* (U.S. Patent No. 5,521,288). The Examiner relies on Linsley *et al.* for teaching that "monoclonal antibodies to CD28 can be employed to treat various autoimmune disorders, including diabetes mellitus (see entire document, in particular, column 36 lines 36-43)." The Examiner notes that the instant claims recite a method comprising administering an antigen binding portion of an anti-CD28 antibody, and states that in the administration of an intact antibody molecule, as taught by Linsley *et al.*, the antigen binding portion would inherently also be administered. The Examiner includes claims 6, 7, 14 and 15 and states that, as evidenced by Paul (Fundamental Immunology, 1999, page 451), CD28 is expressed on both CD4+ and CD8+ cells, and thus an antibody that blocks signaling via CD28 would inherently downmodulate an immune response mediated by both CD4+ and CD8+ cells.

Applicants respectfully traverse this rejection. Claims 1, 2, 6-10 and 14-16 are not anticipated by Linsley *et al.* since the reference fails to teach or suggest each and every element of the claimed invention.

Applicants note that the term "comprising" relates to the method steps of the claimed invention, and not to the composition being administered. The composition which is administered according to the instant claims is an "antigen binding portion of an anti-CD28 antibody." The term "antigen binding portion" is defined in the specification at page 9, second paragraph, as follows:

> The term "antigen-binding portion", as used herein, refers to one or more ***fragments of an antibody*** that retain the ability to specifically bind to an antigen (*e.g.*, human CD28). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. ***Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include*** (i) a ***Fab fragment***, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a ***F(ab')$_2$ fragment***, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a ***Fd fragment*** consisting of the VH and CH1 domains; (iv) a ***Fv fragment*** consisting of the VL and VH domains of a single arm of an antibody, (v) a ***dAb fragment*** (Ward *et al.*, (1989) *Nature* 341:544-546), which consists of a VH domain; and (vi) an isolated complementarity determining region (***CDR***). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as ***single chain Fv*** ("scFv"); see *e.g.*, Bird *et al.* (1988) *Science* 242:423-426; and Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883) . Such single chain antibodies (scFvs) are preferred molecules intended to be encompassed within the term "antigen-binding portion" of an antibody. Other forms of single chain antibodies, such as ***diabodies*** are also encompassed. Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see *e.g.*, Holliger, P., *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; Poljak, R.J., *et al.* (1994) *Structure* 2:1121-1123). Preferably, the antigen-binding fragments do not cross-link the antigen to which they bind.

Thus, as defined in the current specification, an "antigen-binding portion" of an anti-CD28 antibody is an anti-CD28 ***antibody fragment***, and excludes an intact antibody molecule. Therefore, the antigen binding portion encompassed by the claims would not inherently also be administered via administration of an intact antibody molecule. However, in the interest of expediting prosecution, claims 1 and 9 have been amended to specify administration of "an ***isolated*** antigen binding portion" of an anti-CD28 antibody, thereby clarifying that intact, whole antibodies are excluded from the scope of the claimed methods.

Moreover, Linsley *et al.* fail to teach or suggest an isolated antigen binding portion of an anti-CD28 antibody that ***blocks signaling via CD28 in vivo***, and ***thereby downmodulates an***

autoimmune response. The instant claims are drawn to a therapeutic method for treating an autoimmune disorder and are, therefore, implicitly methods necessarily carried out *in vivo*. Linsley *et al.* fail to provide any evidence that an anti-CD28 antibody fragment would block CD28 signaling *in vivo*, and thereby treat an autoimmune disorder. In fact, later published work teaches, to the contrary, that an anti-CD28 Fab fragment does not block CD28 signaling *in vivo* in a mouse model for the autoimmune disorder, graft-versus-host disease (see Yu *et al.*, U.S. Patent Publication No. 2002/0006403).

Accordingly, based at least on the foregoing, claims 1, 2, 6-10 and 14-16 are novel in view of Linsley *et al.* Applicants, therefore, respectfully request the Examiner to reconsider and withdraw the rejection of claims 1, 2, 6-10 and 14-16 under 35 U.S.C. § 102(e) as anticipated by Linsley *et al.*, as evidenced by Paul.

Rejection of Claims 1-4, 6-12, 14-20 and 22-24 Under 35 U.S.C. § 102(e)

Claims 1-4, 6-12, 14-20 and 22-24 are rejected under 35 U.S.C. § 102(e) as being unpatentable over Yu *et al.* (U.S. Patent Publication No. 2002/0006403) as evidenced by Paul (Fundamental Immunology, 1999, page 451). The Examiner relies on Yu *et al.* for teaching "inhibiting an immune response in a subject by administering an anti-CD28 antibody (see entire document, in particular, claim 1 and paragraph 0013)." The Examiner states that Yu *et al.* further teach that the subject may have an autoimmune disease, such as diabetes mellitus, that the antibody may be human or humanized and that the antibody may consist of an antigen binding region, such as Fab or scFv. The Examiner continues that as evidenced by Paul (Fundamental Immunology, 1999, page 451), CD28 is expressed on both CD4+ and CD8+ cells, and thus an antibody that blocks signaling via CD28 would inherently downmodulate an immune response mediated by both CD4+ and CD8+ cells.

Applicants respectfully traverse the rejection. As discussed above, claims 1, 9 and 17, as amended, are drawn to methods of therapeutically and prophylactically downmodulating an (ongoing) autoimmune response in a subject comprising administering an ***isolated antigen binding portion*** of an anti-CD28 antibody that blocks signaling via CD28 to the subject such that an autoimmune response in the subject is downmodulated.

The primary reference, Yu *et al.*, fails to teach or suggest each and every aspect of the claimed therapeutic method. In particular, Yu *et al.* fails to teach the claim limitation that an

autoimmune response is downmodulated as a result of the administration of an isolated anti-CD28 antibody fragment *in vivo*. Indeed, Yu *et al.* provides no evidence that an isolated antigen binding portion of an anti-CD28 antibody blocks signaling via CD28 or blocks T cell responses. With respect specifically to blocking of signaling via CD28 *in vivo*, the Yu *et al.* disclosure provides evidence only that administration of an ***intact anti-CD28 mAb*** (anti-human CD28 mAb 9.3) is effective in the prevention of graft-versus-host disease mediated by human T cells in a mouse model (see Example 9 at page 24, paragraph 0264). In fact, Yu *et al.* expressly contradict the instant claimed invention by providing evidence that an ***anti-CD28 Fab fragment*** is ***not effective*** in preventing the autoimmune graft-versus-host disease in a mouse model and is, therefore, ***not effective*** in blocking CD28 costimulation (see Example 4 at page 22, paragraphs 0246 and 0247). Yu *et al.* thus fails to teach the result required by the instant claims, and therefore does not anticipate the claimed invention.

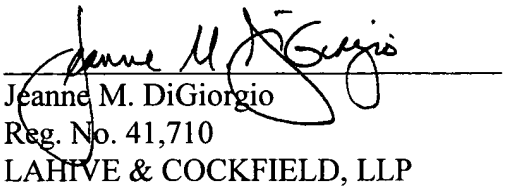
Based at least on the foregoing, the pending claims are patentable in view of the cited references. Applicants, therefore, respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-4, 6-12, 14-20 and 22-24 under 35 U.S.C. § 102(e) as anticipated by Yu *et al.* as evidenced by Paul.

SUMMARY

Based on the foregoing amendments and arguments, reconsideration and withdrawal of all the rejections, and allowance of this application with all pending claims are respectfully requested. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Dated: June 27, 2005

Respectfully submitted by,



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